REMARKS

The Examiner objected to claims 38 and 84 stating that the phrase "the relevance score is displayed as a ***valued,"*** should be replaced by "the relevance score is displayed as a ***value."*** The claims have been amended accordingly. Similar typographical errors in claims 50 and 96 have also been corrected.

The Examiner rejected Claims 1-3, 12-13, 15, 20-22, 24, 26-29, and 55-56 under 35 U.S.C. 102(b) as being anticipated by Cuticchia et al. [CABIOS, 1992, volume 8, pages 467-474]. Applicant traverses the rejection.

Claim 1 is drawn to a computer-implemented method for overlaying gene- or protein-related data on **chromosome maps** to provide a data-enhanced chromosome map as an output. In the current office action, the Examiner states that in the absence of any definition of "chromosome map" in the specification of the current invention, the Examiner is taking a definition from the Collins English Dictionary (2000) as "an accepted meaning of a chromosome map for the purpose of analyzing applicant's argument", that definition being "A graphic representation of the positions of genes on chromosomes, obtained by observation of chromosomal bands ***or by determining the degree of linkage between genes"*** (the Examiner's emphasis).

Applicant submits that even if one accepts the Examiner's definition of a chromosome map, Cuticchia does not teach that chromosome maps are received as an input as required by claim 1 and the claims dependent therefrom. The Examiner points to the first two paragraphs of the subsection "System and methods" beginning on Page 467 and to Example 1 on page 472 as providing this teaching. The cited passages teach that the user may input the results of hybridization experiments (Figure 1), or may input more general chromosome walking information (Figure 2) including the code strings that identify the positions of clones in terms of row and column position in standard database sub-libraries. The Examiner appears to be interpreting either the graphic of Figure 1 or one of the sample screens of Figure 2 as one of the

recited chromosome maps that are input.

First, the position of hybridization for a particular clone and probe in a database is not the position of genes on a chromosome. The row and column at which data is stored in a table does not define the position of a gene on a chromosome.

Second, Figure 1 is an interface for entering hybridization data from various hybridization experiments. The interface allows the user to enter the degree of hybridization between an extract from each of a number of clones and a genetic probe that specifies a gene. The clone is specified by the row in the figure, and the probe is specified by the column, the degree being represented by the shading of the spot at the row and column. Given sufficient hybridization data and additional information the degree of linkage between genes can be determined; however, an interface for entering that data is not a genetic map or the degree of linkage between genes on a chromosome. A stack of lumber can be used to build a house; however, the stack is not the house.

Finally, one of the goals of Cuticchia is to generate the chromosome maps as an output, not input the maps as the Examiner claims. If the map already existed as input, there would be no need for the method in question. Accordingly, Cuticchia does not teach that chromosome maps are received as inputs even with the Examiner's definition of a chromosome map.

Claim 1 also requires that the claimed data items be displayed on one of the chromosome maps to provide a **data-enhanced chromosome map** as an output. The Examiner points to Figure 1, apparently identifying the 2D matrix of circles that may be filled as the recited chromosome map which is "enhanced" by the black, gray or white fills. As noted above, none of the data shown in Figure 1 would satisfy the Examiner's definition of a chromosome map. In the current office action, the Examiner seems to identify the screen of Figure 2B as the recited map which is "enhanced" by the hybridization fill data of Figure 1. As noted above, none of the data shown in Figure 2B would satisfy the Examiner's definition of a chromosome map. Hence, Cuticchia does not teach the display of a data enhanced chromosome map

Further, claim1 requires the provision of an **identifier** specifying a genetic location for each of said data items **on said chromosome maps**. The Examiner points to the paragraph bridging columns 1 and 2 on page 469 of Cuticchia, identifying the code string "L67A12" as the identifier, as it "*specifies the location of the corresponding clone as row A, column 12 of plate 67 within sub-library of chromosomal data*". The recited code string indicates the location of hybridization data for that clone among a matrix of clone-containing wells on a titration plate and the location of where data related to that clone is stored within a database. Neither location is equivalent to the location of data related to the location of a gene on a **chromosome map**, as defined by the Examiner.

Claim 1 also requires that the identifiers be matched to predetermined identifiers on chromosome maps. The Examiner appears to interpret the hybridization measurements indicated graphically in Figure 1 with the predetermined identifiers, as the clones corresponding to those measurements "*are mapped by location identifier (as in Figure 2B of Cuticchia et al.) to locations within the chromosomal library.*" First, the hybridization measurements are not predetermined, as they are experimentally determined data. Second, as noted above, storage locations within the chromosomal library are not locations on chromosomal maps. While one could construct a library with this property, there is no such teaching in the reference.

Still further, claim 1 requires that the data items be reordered to an order matching the order of the predetermined identifiers. In the current office action, the Examiner states that as no specific order is recited, "*ANY order of the predefined identifiers is the order of the predefined identifiers*". The Examiner asserts that the spatial correspondence between hybridization data ("predetermined identifiers") and the cells ("data items") of the matrix of Figure 1 provides the recited reordering. At most, the reference teaches a single step of **ordering** measured data resulting from a microtiter plate experiment to correspond with the positions of the corresponding wells on a graphical representation of the plate, but there is no teaching of any **reordering** of even these types of information, let alone the types specified in the claim.

Accordingly, Applicant submits that claim 1 and the claims dependent therefrom are not anticipated by Cuticchia.

Claims 3, 12, and 15 depend from claim 1 and include additional limitations. The grounds the Examiner presents for rejection of claims 3, 12 and 15 with regard to the additional limitations all rest on the Examiner's interpretation of Figure 1 and/or Figure 2 as showing chromosome maps. As discussed above, neither of the cited figures shows a "chromosome map" that satisfies the Examiner's chosen definition of the term. Hence, there are additional grounds for allowing claims 3, 12 and 15.

Claim 13 depends from claim 1 and additionally requires that identifiers **specifying a genetic location for each of said data items** be selected from published gene identifiers and symbols. In this office action, the Examiner suggests that as the code strings (e.g. L67A12) that the Examiner interprets to be the recited identifiers are made up of letters and numbers (symbols) and are published (in the cited paper by Cuticchia), the additional limitation is taught.

The code strings specify the locations of the results of a hybridization experiment in a database. They do not specify a genetic location for a data item other than data specifying a genetic location on chromosome map. It should be noted that the Examiner has already taken the position that these strings specify a chromosome map, and hence, the identifiers suggested by the Examiner could not be the identifiers in question. Furthermore, the identifiers are not gene identifiers. Finally, the identifiers are not selected from published gene identifiers, since even with the Examiner's interpretation, the identifiers were not published when selected. Hence, there are additional grounds for allowing claim 13.

Claim 15 depends from claim 1 and further requires a relational database which stores a set of cross-referenced **tables for matching said identifiers (as they are read) with said predefined identifiers** through standard database queries. The Examiner points to the title and to Figure 1 of Cuticchia for this teaching, stating "*hybridization data are cross-referenced with the chromosomal contig data*". At most, Cuticchia teaches a database that matches names

("identifiers") like L67A12 with hybridization measurements, but those names are not the recited identifiers (as they don't specify locations on a chromosome map) and the hybridization measurements are not the recited predetermined identifiers (as they are not predetermined). Hence, there are additional grounds for allowing Claim 15.

Claim 20 depends from claim 1 and further requires that co-location values be **statistically assessed** and that the **assessed co-location statistical significance be displayed** along side said gene- or protein-related data**.** The Examiner identifies the d(a,b) values of Cuticchia as the co-location values. Even with this definition, the Examiner has not pointed to any teaching of statistical assessment of d(a,b) values, or of the display of any type of statistical significance, or even of the display of the d(a,b) values. Hence, there are additional grounds for allowing claim 20.

Claim 21 depends from claim 1 and further requires that additional information characterizing the gene- or protein-related data be displayed along side of said display of that data and positioned relative to the respective locations on the chromosome map of the respective genes characterized by that data. The Examiner identifies the d(a,b) values as the additional information. As noted above with respect to claim 20, there is no display of d(a,b) values in Cuticchia. Hence, even with the Examiner's definition, there are additional grounds for allowing claim 21 and the claims dependent therefrom.

Claim 22 depends from claim 21 and additionally requires that the additional information comprise annotations. The Examiner identifies the "hybridization data" of Figure 1 as the recited annotations. However, the Examiner has already interpreted the hybridization data (indicated in Figure 1 by the black, gray or white fills) as the recited data items received, that are to be enhanced. Applicant submits that the "hybridization data" cannot be that data and also be the additional information characterizing that data. Hence, there are additional grounds for allowing claim 22 and the claims dependent therefrom. Essentially the same additional grounds exist for allowing claim 55 and the claims dependent therefrom.

With respect to Claim 26, the Examiner interprets Figure 1 as the scatter plot recited in the claim. The data to be displayed in the scatter plot is different from the data that specifies the genetic locations on the chromosome maps. The Examiner has already identified Figure 1 as the chromosome map, and hence, even with the Examiner's definition, the limitations of Claim 26 are not met. Accordingly, there are additional grounds for allowing Claim 26.

The Examiner rejected claims 4-11 under 35 U.S.C. 103(a) as being unpatentable over Cuticchia et al. as applied to claims 1-3, 12-13, 15, 20-22, 24, 26-29, and 55-56 above in further view of Koleszar et al. [US Patent 6,519,583; issued 11 February 2003; filed 27 July 1999]. Applicant traverses the rejection.

The Examiner states that Cuticchia teaches the limitations of claims 4-11, except for the limitations requiring particular display features. The Examiner looks to Koleszar, whose teachings are directed towards the graphical display of computer-based biomolecular sequence information for the missing teachings. The Examiner maintains that it would have been obvious to apply the display features taught by Koleszar to the method of Cuticchia to display "the genomic data in a more convenient and user-friendly format [see, for example, column 2, lines 5-9 of Koleszar et al.]".

As noted above with respect to claim 1, from which claims 4-11 depend, Cuticchia does not teach the base claim limitations regarding the recited inputs, the desired output, identifiers, identifier matching, and data reordering. Koleszar does not provide the missing teachings. In addition, the compression is applied to the gene- or protein-related data of Claim 1. As noted above, Cuticchia does not provide a display of such data; hence, there is no display to apply the zooming operation identified by the Examiner as compressing the data in question. Accordingly, Applicant submits that the Examiner has not made a *prima facie* case for obviousness with respect to claims 4-11.

With respect to claim 5, which requires zooming to display an enlarged view of additional detail, the issue is not whether Koleszar "has the ability to" zoom, but whether the display of

Figure 1 of Cuticchia would benefit from the application of a zoom feature. However, there is no detail in Figure 1 that is not visible from the current Figure 1. Furthermore, the data in Figure 1 has been identified by the Examiner as the chromosome map, and hence, cannot be the data in question. Hence, nothing is gained by providing the zoom feature of Koleszar to the display of Cuticchia. Accordingly, there are additional grounds for allowing claim 5.

The grounds the Examiner presents for rejection of claim 7 with regard to the additional limitations rests on the Examiner's interpretation of Figure 1 and/or Figure 2 as showing chromosome maps. As noted above, these figures are not chromosome maps even with the Examiner's definition of a chromosome map. Hence, there are additional grounds for allowing claim 7, for the same reasons discussed above with respect to claim 1.

With respect to claim 11, which requires the display of **popup dialogs,** the Examiner interprets buttons at the top of Figures 4A and 4B of Koleszar to be "pop-up menus" that operate to achieve the same function (of displaying additional detail of a selected portion of the display) as the recited popup dialogs. First, the claim limitation is a structural limitation, not a functional one, so the specific components recited must be taught by, or be obvious in view of, the cited reference. Second, the buttons of Koleszar do not have the essential features of popup dialogs, as they do not "popup" i.e. they are not temporary windows that suddenly appear in the foreground of a GUI (see the definition at http://whatis.techtarget.com/definition/0,,sid9_gci212806,00.html) and they do not "dialog" in the sense of requesting from the user or communicating information to the user in a reciprocal fashion. (See http://en.wikipedia.org/wiki/Dialog_box which describes a dialog window as enabling "*reciprocal communication or dialog between a computer and its user. It may communicate information to the user, prompt the user for a response, or both".)* Third, as noted above with respect to claim 5, Figure 1 of Cuticchia would not benefit from the addition of popup dialogs or other means of displaying additional detail of a selected portion of the display. Hence, there are additional grounds for allowing claim 11.

The Examiner rejected Claims 14, 16-19, 23, 25, 30-37, 40-43, 80-83, and 86-89 under 35 U.S.C. 103(a) as being unpatentable over Cuticchia et al. as applied to claims 1-3,

12- 13, 15, 20-22, 24, 26-29, and 55-56 above in further view of Schena et al. [PNAS, 1996, volume 93, pages 10614-10619]. Applicant traverses the rejection.

The Examiner states that Cuticchia teaches all the limitations of base claim 1, from which claims 14, 16-19, 23, 25, 30-37, 40-43 depend, and most of the limitations of base claim 80, from which claims 82-83 and 86-89 depend, looking to Schena for the additional limitations. The Examiner maintains that it would have been obvious to apply the teachings of Schena to those of Cuticchia "because both studies analogously pertain to viewing data regarding chromosomal properties in the form of matrices".

As noted above with respect to claim 1, Cuticchia does not teach the limitations common to claims 14, 16-19, 23, 25, 30-37, 40-43, 80-83, and 86-89 regarding the recited inputs, the desired output, identifiers, identifier matching, and data reordering. Schena does not provide the missing teachings. Furthermore, the Examiner has identified the matrices of expression data as the genetic map. Accordingly, Applicant submits that the Examiner has not made a *prima facie* case for obviousness with respect to claims 14, 16-19, 23, 25, 30-37, 40-43, 80-83, and 86-89.

With respect to Claim 14, the Examiner has already identified the gene identifiers as the data strings such as "L67A12" in rejecting Claim 13, from which Claim 14 depends. These strings are clearly not chosen from the symbols recited in Claim 14. Hence, there are additional grounds for allowing Claim 14.

Claim 16 additionally requires that each said row of the expression matrix contains data values for a particular gene or protein across a set of measured samples, and that results of each said measured sample be provided by data in respective columns of said matrix. The Examiner points to the matrix displays of Schena as providing these teachings, but Applicant finds no teaching therein that the rows and columns contain the values specified. Table 1, for example, shows that the same row may contain values for different genes (Row 20 has clone B1 and B23) and there is no teaching that each column is limited to measurements from a single sample. In addition, the only matrix identified in Cuticchia is the structure that the Examiner identifies as

the chromosome map, so that structure could not be the matrix in question. Hence, there are additional grounds for allowing claim 16 and the claims dependent therefrom.

With respect to Claim 17, the Examiner has already identified expression matrices as chromosome maps; hence, the Examiner cannot now identify such matrix as the claimed gene- or protein-related data that does not specify genetic location on a protein map. Hence, there are additional grounds for allowing Claim 17.

Claim 18 includes a similar requirement to that of claim 16, that each row of the matrix be associated with a particular gene, with data in the respective row being associated with said particular gene. Hence, the same additional grounds exist for allowing claim 18 as discussed above with respect to claim 16.

Claim 23 depends from claim 21, and hence, requires the display of **additional information** characterizing the gene- or protein-related data along side of said display of that data and positioned relative to the respective locations on the chromosome map of the respective genes characterized by that data. As discussed above with respect to claim 21, this is not taught by Cuticchia. Schena does not provide the missing teachings. Hence, there are additional grounds for allowing claim 23.

Claim 30 depends from claim 18 and additionally requires that row vectors of the values in the rows of the matrix be calculated; using an auxiliary process to obtain cluster data for said row vectors; and **displaying said cluster data along side said display** of said arbitrary gene- or protein-related data. The Examiner points to Figures 1 and 2 of Schena, interpreting the left panel Figure 2 as showing cluster data obtained from the values in Figure 1. The display along side the left panel of Figure 2 is another display of "cluster data" from a second experiment, not the data from which the left panel data was calculated. Hence, there are additional grounds for allowing claim 30 and the claims dependent therefrom.

Claims 32 and 33 depend from claim 30 and additionally require that cluster data be

displayed in a single column or a multi-column matrix respectively, **adjacent** each matrix of gene- or protein-related data. In the current office action, the Examiner points to the matrices of Figures 1 and 2 of Schena, stating that the display of "*the level of gene expression (i.e. cluster data) ...adjacent to (i.e. on top of) the matrix using a series of colors*" provides the recited teaching. Even if the color coding of cells in a matrix were taken to be a display of data "on top of those" cells, such positioning is not "adjacent". Hence, there are additional grounds for allowing claims 32 and 33.

Claim 34 depends from claim 1 and additionally requires that the gene- or protein-related data comprises a matrix of at least one microarray of gene expression data, wherein (1) **each row of the matrix is associated with a particular gene,** and wherein (2) **each column of the matrix is associated with a microarray experiment**, wherein (3) a portion of the total number of columns is associated with experiments taken **from normal, healthy tissue**, and another portion of the total number of columns is associated with experiments taken **from tissue exhibiting an abnormality**, said method further comprising (4) dividing the matrix into two smaller matrices with **a first matrix containing the columns associated with normal experiments and a second matrix containing the columns associated with abnormal experiments,** and wherein said matching and displaying are performed with regard to both first and second matrices.

With respect to limitation (1), as noted above with respect to claim 16, Schena does not teach that each row of any of the matrices is associated with a particular gene. With respect to limitation (2), not only does Schena not teach that each column is associated with a microarray experiment but the Examiner takes each cell in the matrix to be associated with its own particular experiment, so each column must be associated with many different experiments.

With respect to limitation (3), the Examiner states that the columns in Figure 1A relate to normal tissue, as no heat shock is applied, while the columns in Figure 2A relate to "abnormal" tissue as heat shock is applied. Applicant submits that the claim uses the word "healthy" to qualify "normal" and specifies that the other category of interest is data from experiments taken from **tissue exhibiting an abnormality**. The distinction is not between tissues which are or are

not subjected to abnormal conditions (heat shock) in the experiments, but between tissues that are intrinsically healthy or unhealthy before any experiments are carried out. Schena does not separate out columns of data in the matrices on the basis of this distinction as recited. With respect to limitation (4), Schena does not divide any matrix into two smaller matrices. At most, Schena uses the data from two matrices (Figure 1A and 1B) of a given size to create one new matrix (Figure 2A) of that same given size. Hence, there are additional grounds for allowing claim 34 and the claims dependent therefrom.

Claim 36 depends from claim 34 and additionally requires that a **relevance score** be calculated for at least one row of the matrices by comparing expression values in the first matrix with expression values in the second matrix, and **displaying** at least one calculated relevance score **along side** the row to which each pertains. The Examiner identifies the differential expression profiles in Figure 2A of Schena as relevance scores. Even if the term "relevance score" were taken to encompass differential expression profiles rather than measures of *the separation value of the particular gene being analyzed*, as taught in the specification of the current invention (paragraph 0094), at most Schena displays expression values as the colors of matrix cells themselves, not along side any rows of cells, as the claim recites. Hence, there are additional grounds for allowing claim 36 and the claims dependent therefrom.

Claim 41 depends from claim 36 and additionally requires that relevance scores be calculated and displayed in a binary code. The Examiner points to the binary codes in Table II in column 1 on page 472 of Cuticchia as providing this teaching. These codes are simply representations of the results of hybridization experiments and are not the results of **any calculation**. Hence, there are additional grounds for allowing claim 41.

Claim 42 depends from claim 36 and additionally requires that a plurality of relevance scores be calculated, said method further comprising **defining a relevance density score** based upon **distances between genetic locations and relevance scores**, and identifying **chromosomal locations** containing relevance density scores greater than or equal to the defined relevance density score. The Examiner points to Figure 1 of Cuticchia as providing these teachings,

identifying the shadings of the circles as intervals of density scores. First, the shadings represent the presence of hybridization, the absence of hybridization, and the absence of a clone. No **densities** are involved. Second, the "hybridization distances d(a,b)" represent differences between profiles, not distances between genetic locations and relevance scores. Third, the locations indicated in the figure are not chromosomal locations.

In the current office action, the Examiner appears to respond to the first and second points above *"the difference in hybridization profile between clones a and b, d(a,b), also alludes to distance value because it is also an indicator of overlap (and thus relative location) between two clones. As a result, higher values of d(a,b) on the matrix of Figure 1 of Cuticchia et al. signify higher relevance density scores.* The Examiner has already interpreted the ratios of expression values from different experiments in Schena as relevance scores. The "ratio" interpretation appears to Applicant to be inconsistent to the Examiner's subsequent interpretation in terms of d(a,b) values. The Examiner has not responded to the third point regarding chromosomal locations. Hence, there are additional grounds for allowing claim 42

Claim 43 depends from claim 36 and additionally requires that the relevance scores be filtered by setting at least one relevance score limit value and displaying **only those relevance scores which are greater than or equal to at least one relevance score limit value**. The Examiner points to Figure 2 of Schena as providing this teaching, interpreting the color coding of data values in the cells of the matrix as filtering relevance scores between limit values. However, the claim also requires that data be excluded from display if the scores are less than one limit value. The only teaching of any data exclusion is in the figure legend, which teaches that some data values (each value being the average from two experiments) are not shown, based on the *relative spread* of results between those two experiments. This is not equivalent to teaching exclusion based on the average data value being less than any threshold value. Hence, there are additional grounds for allowing claim 43.

Applicant submits that claim 80 and the claims dependent therefrom should be allowed for the same reasons discussed above with respect to claim 34, that the same additional grounds

exist for allowing claim 82 and the claims dependent therefrom as those discussed above with respect to claim 36, and that the same additional grounds exist for allowing claims 88 and 89 as those discussed above with respect to claims 42 and 43 respectively.

The Examiner rejected Claims 38 and 84 under 35 U.S.C. 103(a) as being unpatentable over Cuticchia et al. in view of Schena et al. as applied to claims 1-3, 12-19, 20-37, 40-43, 55-56, 80-83, and 86-89 above, and further in view of McCully [US Patent 4,383,994 issued 17 May 1983; filed 19 January 1982]. Applicant traverses the rejection.

The Examiner states that the combination of Cuticchia and Schena teaches all the limitations of claims 38 and 84 except for requiring that the relevance score comprise a "p value" and the relevance score be displayed as a value calculated by (-log p value). The Examiner looks to McCully for the additional limitations. The Examiner maintains that it would have been obvious to apply the teachings of McCully to those of Cuticchia/Schena to provide "improved and more advanced statistical analysis".

First, as noted above with respect to claims 1 and 80, from which claims 38 and 84 respectively depend, the combination of Cuticchia/Schena fails to teach the limitations regarding the recited inputs, the desired output, identifiers, identifier matching, and data reordering. McCully does not provide the missing teachings.

Second, as noted above with respect to claims 36 and 82, from which claims 38 and 84 respectively also depend, the combination of Cuticchia/Schena fails to teach the requirement that a relevance score be calculated for at least one row of the matrices by comparing expression values in the first matrix with expression values in the second matrix, and **displaying at least one calculated relevance score along side the row to which each pertains**. Even if the term "relevance score" were taken to encompass differential expression profiles, at most Schena displays expression values as the colors of matrix cells themselves, not along side any rows of cells, as the claim recites. McCully does not provide the missing teachings.

Accordingly, Applicant submits that the Examiner has not made a *prima facie* case for obviousness with respect to claims 38 and 84.

The Examiner rejected Claims 39 and 85 under 35 U.S.C. 103(a) as being unpatentable over Cuticchia et al. in view of Schena et al. as applied to claims 1-3, 12-19, 20-37, 4043, 55-56, 80-83, and 86-89 above, and further in view of Ben-Dor et al. [Genome Research, 2000, volume 10, pages 365-378]. Applicant traverses the rejection.

The Examiner states that the combination of Cuticchia and Schena teaches all the limitations of claims 39 and 85 except for the calculation of a plurality of relevance scores and their display as a line map. The Examiner looks to Ben-Dor for the missing teachings. The Examiner maintains that it would have been obvious to apply the teachings of Ben-Dor to the method of Cuticchia/Schena as "*an alternate means of analyzing the mappings of chromosomes*".

First, as noted above with respect to claims 36 and 82, from which claims 39 and 85 respectively depend, the combination of Cuticchia/Schena fails to teach the limitations regarding the recited inputs, the desired output, identifiers, identifier matching, and data reordering. Ben-Dor does not provide the missing teachings.

Second, the Examiner has not suggested any benefit that would be gained by the method of Cuticchia/Schena in applying the "alternate means" of Ben-Dor. The number of possible alternate means of analyzing gene mappings is very large, and there is no obvious reason why the means of Ben-Dor would confer a particular advantage to Cuticchia/Schena absent the present application as a guide. In the current office action, the Examiner again states "*as line maps are an alternate means for mapping the same information using a substitute (are equivalents), it is adequate for an obviousness prior art rejection*". Applicant submits that to sustain an obviousness rejection in view of a combination of prior art references the Examiner must show that there is some **motivation** in the art that would cause someone of ordinary skill to combine the references, and that in making the combination, there was a reasonable expectation of success. A proper analysis in this situation requires, *inter alia*, consideration of two factors: (1)

whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success... Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442(CAFC 1991). Applicant maintains that there is no suggestion in this case founded in prior art. Accordingly, Applicant submits that the Examiner has not made a *prima facie* case for obviousness with respect to claims 39 and 85.

The Examiner rejected Claims 44-47, 49, 52-54, 90, 92-93, 95, and 98-101 under 35 U.S.C. 103(a) as being unpatentable over Cuticchia et al. in view of Schena et al. as applied to claims 1-3, 12-19, 20-37, 40-43, 55-56, 80-83, and 86-89 above, and further in view of Pollack et al. [Nature Genetics, volume 23, 1999, pages 41-46]. Applicant traverses the rejection.

The Examiner states that Cuticchia teaches all the limitations of claims 44-47, 49, 52-54, 90, 92-93, 95, and 98-101 except those relating to abnormal copy numbers, or the one-to-one correspondences between the third and fourth matrices and the first and second matrices, respectively. The Examiner looks to Schena as teaching the correspondences between matrices, but not that these additional matrices are related to chromosomal copy numbers. The Examiner looks to Pollack for the missing teachings. The Examiner maintains that it would have been obvious to "*to modify the chromosomal mapping techniques of Cuticchia et al. and Schena et al., by use of the color coded heat map plots of Pollack et al. wherein the motivation would have been that the use of such plots allow more conveniently acquired and well resolved data [see lines 13-17 of abstract on page 41 and Figure 5a of Pollack et al.]*" and to further "*modify differential gene expression to analyze abnormalities as in Cuticchia et al. and Schena et al. by use of the disease analysis by chromosomal copy number analysis as in Pollack et al. because it is obvious to substitute known elements in the prior art to yield a predictable result*".

As noted above with respect to claims 34 and 80, from which claims 44-47, 49, 52-54, 90

and 92-93 respectively depend, the combination of Cuticchia and Schena fails to teach the limitations regarding the recited inputs, the desired output, identifiers, identifier matching, data reordering, or the details regarding the row and column data, normal and abnormal tissue, and the matching and displaying being performed with regard to two matrices that are divided out from a single original matrix. Pollack does not provide the missing teachings. Accordingly, Applicant submits that the Examiner has not made a *prima facie* case for obviousness with respect to claim claims 44-47, 49, 52-54, 90 and 92-93 44, 46-47, 90 and 92-93.

Claim 45 additionally requires that the chromosomal copy number abnormality data be displayed in third and fourth matrices, wherein each value in the third matrix is matched with the expression value in the first matrix having the same row and column location, and wherein each value in the fourth matrix is matched with the expression value in the second matrix having the same row and column location. The Examiner points to Figures 1 and 2 of Schena for this teaching, identifying the "matrices" in Figure 1 as first and second matrices and those in Figure 2 as the third and fourth matrices. However, the data in the "third" matrix relates to data from both "+ Heat Shock" and "-Heat Shock" experiments, i.e. to both first and second matrices, and the data in the "fourth" matrix relates to data from another pair of experiments involving Phorbol Ester, that are not shown anywhere in matrix form, and are certainly not shown in the second matrix.

In the current office action, the Examiner points to "Microarray Preparation" [singular]) in column 2 on page 10614 of Schena as teaching "*the same microarray setup is used four times (no Heat shock, Heat Shock, no phorbol ester, phorbol ester). Thus, each of the four microarray setups corresponds to one of the four matrices wherein the location for each cell (i.e. row, column) within the microarray setup corresponds to the same gene expression analysis in each of the four matrices.*" At most, this suggests that the sample compositions within the cells at corresponding positions in four microarrays are the same. However, claim 45 requires that values in third and fourth matrices are matched not with corresponding samples but with corresponding expression values in first and second matrices respectively. The values in the fourth matrix (Figure 2B) are not matched with the expression values in the second matrix

(Figure 1B). Accordingly, there are additional grounds for allowing claim 45.

Claims 46 and 92 also require that the chromosomal copy number abnormality data be provided in columns interlaced with the columns of expression data in the first and second matrices. The Examiner points to Cuticchia (paragraph bridging columns 1-2 on page 471) as providing this teaching. The cited passage teaches that data may be added to a database, to enter comments or other general information about clones, but it does not teach that data is provided in interlaced columns in matrices as required by the claim. In the current office action, the Examiner also points to Figure 5a of Pollack as teaching annotating matrices with chromosomal abnormality data. The cited figure shows annotations superimposed on an image of an array, but does not show any column interlacing of data as recited. Accordingly, there are additional grounds for allowing claims 46 and 92.

Claims 53 and 54 depend from claim 45 through claim 49 and include additional limitations corresponding to those of claim 42 and 43 respectively, regarding relevance density scores and filtering. As noted above with respect to claims 42 and 43, the combination of Cuticchia/Schena does not teach the additional limitations. Pollack does not provide the missing teachings. Accordingly, there are additional grounds for allowing claims 53 and 54.

Claim 101 includes several limitations regarding the displayed output or the matching of received identifiers with predefined identifiers, corresponding to those of claims 1 and 80. As noted above with respect to claims 1 and 80, the combination of Cuticchia/Schena fails to teach these limitations. Pollack does not provide the missing teachings. Claim 101 additionally includes limitations corresponding to those of claim 45. As noted above with respect to claim 45, the cited prior art does not teach these additional limitations. Accordingly, Applicant submits that the Examiner has not made a *prima facie* case for obviousness with respect to claim 101 and the claims dependent therefrom.

Claims 95 and 98-100 depend from claim 101 and include additional limitations corresponding to those of claims 36, 39, 42 and 43. As noted above with respect to claims 36, 39,

42, and 43, the combination of Cuticchia/Schena does not teach the additional teachings. Pollack does not provide the missing teachings. Accordingly, there are additional grounds for allowing claims 95 and 98-100.

The Examiner rejected claims 50 and 96 under 35 U.S.C. 103(a) as being unpatentable over Cuticchia et al. in view of Schena et al. in view of Pollack et al. as applied to claims 1-3, 12-37, 40-47, 49, 52-56, 80-83, 86-89, 92-93, 95, and 98-101 above, and further in view of McCully [US Patent 4,383,994 issued 17 May 1983; filed 19 January 1982]. Applicant traverses the rejection.

The Examiner states that the combination of Cuticchia, Schena and Pollack teaches all the limitations of claims 50 and 96 except for requiring that the relevance score comprise a "p value" and the relevance score be displayed as a value calculated by (-log p value). The Examiner looks to McCully for the additional limitations. The Examiner maintains that it would have been obvious to apply the teachings of McCully to those of Cuticchia/Schena to provide "improved and more advanced statistical analysis".

First, as noted above with respect to claims 1 and 101, from which claims 50 and 96 respectively depend, the combination of Cuticchia/Schena fails to teach several of the base claim limitations. In the case of claim 50, which also depends from claim 49, the combination of Cuticchia/Schena also fails to teach the limitations of that intervening claim 49. Neither Pollack nor McCully provide the missing teachings.

Second, the additional limitations of claims 50 and 96 correspond to those of claim 38. As discussed above with respect to claim 38, the combination of Cuticchia/Schena fails to teach the requirement regarding the display of at least one calculated relevance score along side the row to which each pertains. Neither Pollack nor McCully provide the missing teachings. Accordingly, Applicant submits that the Examiner has not made a *prima facie* case for obviousness with respect to claims 50 and 96.

The Examiner rejected claims 48, 51, 94, and 97 under 35 U.S.C. 103(a) as being unpatentable over Cuticchia et al. in view of Schena et al. in view of Pollack et al. as applied to claims 1-3, 12-37, 40-47, 49, 52-56, 80-83, 86-89, 92-93, 95, and 98-101 above, and further in view of Ben-Dor et al. [Genome Research, 2000, volume 10, pages 365-378]. Applicant traverses the rejection.

The Examiner states that the combination of Cuticchia, Schena and Pollack teaches all the limitations of claims 48, 51, 94, and 97 except for the use of line maps. The Examiner maintains that it would have been obvious to apply the teachings of Ben-Dor to the method of Partridge/Reeves as "an alternate means of analyzing the mappings of chromosomes".

As noted above with respect to claims 44 and 90, from which claims 48 and 94 respectively depend, and claim 34, from which claim 51 depends, the combination of Cuticchia/Schena fails to teach many of the base claim limitations. Neither Pollack nor Ben-Dor provide the missing teachings. In addition, the Examiner has not pointed to any advantage in using this alternate means of analyzing the mappings over any of the other possible alternate means in the prior art, absent the present application as a guide. Accordingly, Applicant submits that the Examiner has not made a *prima facie* case for obviousness with respect to claims 48, 94 and 51.

As noted above with respect to claim 95, from which claim 97 depends, the limitations corresponding to those of claim 36 regarding relevance scores are not taught by the combination of Cuticchia, Schena and Pollack. Ben-Dor does not provide the missing teachings. Accordingly, Applicant submits that the Examiner has not made a *prima facie* case for obviousness with respect to claim 97.

Respectfully Submitted,

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